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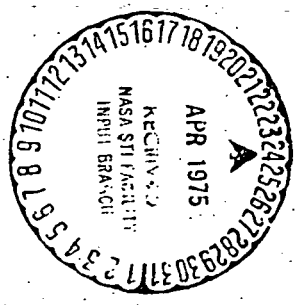
TITLE: Cardiovascular Effects of Variations in Habitual Levels of Physical Activity

Codirectors: C. Gunnar Blomqvist, MD, PhD, Associate Professor of Medicine and Physiology (Principal Investigator)

and

Jere H Mitchell, MD, Professor of Medicine and Physiology

Institution: Pauline and Adolph Weinberger Laboratory for Cardiopulmonary Research
Department of Internal Medicine
The University of Texas Health Science Center at Dallas
Southwestern Medical School
5323 Harry Hines Boulevard
Dallas, Texas 75235



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1. OBJECTIVES

The primary objective of this project was to elucidate mechanisms involved in human cardiovascular adaptation to stress, particularly adaptation to different levels of physical activity. A secondary objective was to develop quantitative noninvasive methods for evaluation of cardiovascular function during stress in normal subjects and in individuals with latent or manifest cardiovascular disease.

2. BRIEF DESCRIPTION

The program has been focused on human adaptation to stress but the objectives have required a combination of studies ranging from basic to applied physiology and clinical investigation. Subprojects fall into the following broad categories:

1. Cardiovascular effects of changes in the habitual level of physical activity.
2. Regulation of cardiovascular function during stress.
3. Development of noninvasive methods for evaluation of cardiovascular function, including both electrocardiographic and hemodynamic methods.
4. Cardiovascular studies in chronically-instrumented dogs.

3. RESULTS

Results of the studies performed with support from this grant have been documented in detail and published in a series of 25 papers and 28 abstracts. Additionally, 4 papers have been submitted for publication. The following report provides a summary of the most significant findings.

3.1.0 - Cardiovascular effects of changes in the habitual level of physical activity.

Basic cardiovascular adaptation to changes in the level of physical activity have been studied both in experimental animals and in human subjects.

3.1.1 - Animal studies on Cardiovascular Adaptation to Different Levels of Physical Activity

To investigate the effects of physical training on cardiac dimensions and function, eight dogs were exercised for 12 weeks by treadmill running 1 hour/day, 5 days/week. Five dogs were confined in cages as controls for a 8-week period. Heart rates were monitored by telemetry during rest and exercise. Maximum QRS spatial magnitudes were calculated from records of McFee lead electrocardiograms. Left ventricular end-diastolic dimensions were determined radiographically by the bead and clip technique. No statistically significant changes occurred during the control period. Training produced satistically significant decreases in heart rate at rest (72 beats/min to 49 beats/min, $P<0.005$) and at a standard work load of 6.1 mph on a level treadmill (205 beats/min to 158 beats/min, $P<0.005$) and statistically significant increases

in work load (5.4 mph to 9.1 mph, $P<0.005$) at a standard heart rate of 194 beats/min. Improvements were rapid during the first 4 weeks of training but gradual during the remaining 8 weeks. Training caused small but statistically significant increases in left ventricular end-diastolic wall thickness (8.7 mm to 9.3 mm, $P<0.025$), estimated left ventricular mass (83.6 g to 91.2 g, $P< 0.01$), and maximum (McFee) WRS spatial magnitude (4.0 mv to 4.8 mv, $P<0.05$).

3.1.2 - Physical training in patients with heart disease.

The effect of physical training in patients with coronary heart disease has been studied extensively during the past few years. Much less is known about the response to training in other forms of cardiovascular disease. A study of training effects in children who have had complete anatomical correction of congenital lesions was performed in collaboration with Dr. W. W. Miller and his associates in the Division of Pediatric Cardiology, Southwestern Medical School.

Fifteen children with surgically tre ted congenital heart disease had studies of cardiopulmonary function before and after 5 weeks of physical training. Twelve children, 7-15 years old, completed at least 80% of the training. Tests of cardiopulmonary function were within 2 SD of normal in all children except for 2 in whom maximum oxygen consumption (VO_2 max) was subnormal. Significant differences were measured only in hemoglobin one second forced expiratory volume and single breach CO diffusion capacity. VO_2 max increased significantly (11% and 24%) in only 2 individuals. Maximum blood pressure decreased significantly in 8 children, was unchanged in 3, and increased significantly in 1. An identical training program produced a 10% increase in maximal oxygen uptake in a matched control group of 12 normal children. This study suggests that either 1) the training requirement is longer for children with corrected congenital lesions than for normal children or 2) a residual impairment in cardiopulmonary adjustment to exercise is present long after successful surgery.

Papers:

Wyatt HL, Mitchell JH: Influences of physical training on the heart of dogs. Circulation Res. 35:883-889, 1974.

Abstracts:

Wyatt, H.L, Mitchell, JH: Effect of chronic level of physical activity on the heart in dogs. Abstr. Clin. Res. 19:26, 1971.

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3.2.0 - Regulation of cardiovascular function during stress.

Studies in this area have dealt with reflex-mediated adaptations to exercise. The diving reflex has been explored in detail. Facial immersion during isometric and dynamic exercise activates a powerful reflex mechanism overriding other regulatory mechanisms and causing a profound bradycardia during both dynamic and isometric exercise. Blood pressure is maintained which is consistent with a marked peripheral base constriction. The diving reflex mechanism has recently

been applied in clinical medicine and found to be of value in the treatment of paroxysmal arterial tachycardia.

Cardiovascular aspects of isometric exercise have been studied in normal subjects and in patients with heart disease. The blood pressure increase induced by isometric exercise has been used as a basis for clinical studies of left ventricular response to increased afterload. Valuable diagnostic information can be derived from left ventricular function curves obtained from direct hemodynamic studies at rest and during exercise. Isometric exercise has also proved to be a convenient means of uncovering latent ventricular arrhythmias and atrial gallops, a phonocardiographic sign of left ventricular dysfunction.

A series of studies in human subjects and experimental animals on muscle afferents based on isometric exercise have also conclusively demonstrated the role of peripheral neural mechanisms in the regulation of the circulatory response to exercise.

Finally, preliminary studies have indicated that the degree of sinus arrhythmia present in normal subjects and in patients with cardiovascular disease may provide at least a semiquantitative measure of vagal tone.

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Mullins, CB and Blomqvist, CG: Isometric exercise and the Cardiac patient. Texas Medicine, 69:53, 1973.

Abstracts:

Houston, J.D., Atkins, JM and Blomqvist, G: Cardiovascular response to isometric forearm contraction. Clin. Res. 18:70, 1970.

Atkins, JM, Houston, JD, Rosenthal, JE, Khero, BA and Blomqvist, G: Cardiovascular response to sustained forearm contraction (handgrip). Clin. Res. 18:296, 1970.

Mullins, CB, Leshin, SJ, Mierzwiak, DS, Matthews, OA and Blomqvist, G: Sustained forearm contraction (handgrip) as a stress test for evaluation of left ventricular function. Clin. Res. 18:322, 1970.

Mullins, CB, Leshin, SJ, Mierzwiak, DS, Matthews, OA and Blomqvist, G: Isometric exercise (handgrip) as a stress test for evaluation of left ventricular function. Circulation 42:111, 1970.

Bergman, SA, Campbell, JK, Burpo, RP, Blomqvist, G., and Wildenthal, K.: The "diving reflex" in man: Its relation to isometric and dynamic exercise. Clin. Res. 20:251, 1972.

Reardon, WC, McCloskey, DI, Mitchell, JH: Cardiovascular response during induced isometric exercise. Clin. Res. 22:298A, 1974.

Harris, MD, Holt, MW, Blomqvist CG: Sinus arrhythmia as an index of vagal tone. Clin. Res. 22:279A, 1974.

3.3.0 - Development of noninvasive methods for evaluation of cardiovascular function.
3.3.1 - Electrocardiographic response to stress.

Diagnostic exercise electrocardiography. Significant progress has been made. A total of 150 normal subjects, 18 to 30 years old, was studied during July-August 1974. Frank lead ECG's were obtained at rest, at several submaximal, and a maximal level in each subject. Data analysis is in progress. The data files now include more than 400 patients with complete tests and coronary angiography and several hundreds of patients with less complete hemodynamic studies but with detailed clinical information. A major collaborative effort has been initiated with Dr. Pipberger and his group at the Veterans Administration Center in Washington, D.C., which is expected to produce a sophisticated multi-dimensional diagnostic analysis system.

An on-line system for averaging, display, and evaluation of the exercise ECG has been completed and is being used clinically.

A large number of studies on various aspects of the ECG response exercise and clinical exercise testing have been undertaken as is evident from the list of publications.

Papers:

Ahmad, M, Blomqvist, CG, Mullins, CB: ECG changes in experimental acute pulmonary hypertension with and without hypoxia. J. Electrocardiology 7:109, 1974.

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Masood, A., Blomqvist G, Alsobrook, H and Mullins CB: Correlation of ECG changes with right ventricular volume in acute pulmonary hypertension. Clin. Res. 20:386, 1972.

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Masood, A., Blomqvist, G, and Mullins, CB: ECG changes during acute pulmonary hypertension with and without hypoxia. Circulation 45-46-II:189, 1972.

Masood, A, Blomqvist, CG, Alsobrook HD, and Mullins CB: Correlation of ECG changes with right ventricular volume in acute pulmonary hypertension. Clin. Res. 20:386, 1972.

Masood, A, Blomqvist CG and Mullins CB: Exercise-induced P wave changes of left atrial overload. Circulation 48:IV-87, 1973.

3.3.2 - Noninvasive hemodynamic studies

A variety of techniques for noninvasive quantitative evaluation of cardiovascular function during stress have been explored.

Phonocardiography during exercise has been applied for the first time. The results of a study of normal subjects and patients with coronary disease suggest that valuable information may be derived from the measurement of the amplitude of the first heart sound during exercise.

Low-frequency precordial vibrations have also been studies by means of apexcardiography. Optimal characteristics of transducers have been defined and the quantitative relation between the apexcardiogram and left venticular pressure has been studied in detail.

A major development effort has resulted in a reliable clinically applicable method for non-invasive measurement of cardiac output, based on the acetylene rebreathing method and mass spectrometer measurement of gas concentrations.

A major effort has also been devoted to echocardiographic studies with a primary objective of defining noninvasive methods for evaluation of left ventricular function. An initial study was based on left ventricular function curves derived from measurements in 14 normal subjects at rest and during lower body negative pressure. Further studies have been performed in patients with unequivocal heart disease (catheterization and angiography).

The search for echocardiographic indices of left ventricular function continues. Mitral valve velocity has been correlated with direct hemodynamic measurements and the results of preliminary studies suggest that changes in mitral valve diastolic velocity may provide an estimate of changes in left ventricular filling pressure.

The group at Southwestern medical School has also assisted the Cardiovascular Laboratory at NASA LBJ Space Center in a series of experiments designed to evaluate the blood pressuring device used during the Skylab missions.

Papers:

Johnson JM, Siegel W and Blomqvist CG: Characteristics of transducers used for recording the apexcardiogram. J. Appl. Physiol. 31:746, 1971.

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Masood A, Blomqvist G, Mullins CB, Willerson JT: Noninvasive evaluation of left ventricular function during lower body negative pressure. J. Appl. Physiol. (Submitted).

Triebwasser JH, Burpo RP, Campbell JC, Reardon WC, Johnson RL Jr, Blomqvist G: Noninvasive determination of cardiac output. J. Appl. Physiol. To be submitted.

Johnson JM, Blomqvist G: The apexcardiogram: Relationship to left ventricular pressure. Cardiovascular Research. To be submitted.

Abstracts:

Matthews, O.A., Blomqvist G, Cohen LS and MUllins CB: Left ventricular function during isometric exercise (handgrip): significance of an atrial gallop (S_4). Circulation 42:III-31, 1970.

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Triebwasser JH, Burpo RP, Campbell JC, Reardon WC, Johnson RL Jr, Blomqvist CG: Non-invasive determination of cardiac output. Amer. J. Cardiol. 31:162, 1973.

Masood A, Mullins CB, Willerson JT, Blomqvist CG: Noninvasive evaluation of left ventricular function by echocardiography during lower body negative pressure (LBNP). Clin. Res. 22:289A, 1974.

Blomqvist CG, Masood A, Mullins CB, Willerson JT: Noninvasive evaluation of left ventricular function by echocardiography during lower body negative pressure (LBNP). XXIX World Congress of Cardiology.

Ahmad M, Nixon JV, Blomqvist CG, Willerson JT: Relation between echocardiographic diastolic mitral valve velocity and left ventricular filling pressure during acute myocardial infarction. Clin. Res. 23:1A, 1975.

3.4.0 - Cardiovascular studies in chronically-instrumented dogs.

For the recent LSI-2 experiment at the LBJ Space Center 4 dogs were instrumented at the Weinberger Laboratory. Two sonocardiometer transducers were implanted in the left ventricle. These transducers continuously measure left ventricular diameter. A high-fidelity Konigsberg solid-state pressure transducer was also implanted in the left ventricle. A Zepeda electromagnetic flow probe was placed around the ascending aorta to measure cardic output and stroke volume. Polyvinyl catheters were inserted into the carotid artery, left atrium, and right atrium. Pacing-electrodes were positioned in the right atrium and right ventricle. All catheters and wires were exteriorized at the back of the neck.

Two animals were selected to be used in the LSI-2 experiment. Recording apparatus was set up from equipment that was available at NASA. The experimental protocol consisted of volume loading the dogs on each day of the simulated 7-day mission. The experiment went well.

3.5.0 - Other results.

The support from NASA during the past 5 year period has also provided invaluable indirect support for the total program at the Weinberger Laboratory for Cardiopulmonary Research. National and International recognition of the work performed at the laboratory in the area of the physiology and pathophysiology of exercise is reflected by a large number of invited review articles published during the grant period.

Reviews:

Markowitz, M, Weidman WH, Blomqvist G, Brandenburg R, Gold W, Gubner RS, Malm JR, Manning J, Neil C, Porter R, Sabiston DC, Schiebler G and Young D: Recreational activity and career choice recommendations for use by physicians counseling physical education directors, vocational counselors, parent, and young patients with heart disease. Circulation 43:459, 1971.

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Blomqvist CG: Exercise testing in rheumatic heart disease. Cardiovascular Clinics. 5:267-287, 1973.

Mitchell JH, and Wildenthal K; Static (isometric) exercise and the heart: physiological and clinical considerations. Ann. Rev. Med. 25:369-381, 1974.

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Blomqvist G: Clinical exercise physiology, in Wenger, N and Hellerstein, H. (Eds.): Rehabilitation of the patient after myocardial infarction. John Wiley & Sons, In press.

Blomqvist G: Computers in clinical cardiology, IN: V. Puddu (Eds.) Cardiologia e'Oggi, Edizione Medico Scientifiche, Torino. In press.